REMARKS

The Advisory Action of May 21, 2007, has been carefully reviewed. It is applicant's understanding that the §112, second paragraph, rejection and the prior art rejections under §102(b) and §103(a) are now withdrawn, and applicant is proceeding in reliance thereof.

In a telephone discussion with the examiner, the undersigned indicated that a correct RCE filed June 14, 2007 but not scanned in properly due to an indexing error on the part of the USPTO EFS had later been correctly scanned in with a request for suspension well after the June 14, 2007, date of filing. This correction however occurred after the mailing of the Office Action of July 3, 2007. Accordingly, the examiner agreed that the Office Action of July 3, 2007, will be vacated and action will be suspended.

Applicant's comments below are directed to the sole outstanding rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Ochoa et al. (US 5,296,353) in view of Babbit et al. (US 5,766,920), Ochoa et al. (US 5,443,983), the acknowledged prior art, Wallace et al., Santamaria et al. and Sekine et al. This rejection is respectfully traversed.

In the Advisory Action, the examiner asserts that "one of ordinary skill in the art is not an automaton". The examiner

may be correct if only one reference is cited and applied that shows some element, but in this case, six references are cited. Three of them use soluble anti-CD3 antibodies, one of them does not use anti-CD3 antibodies. The relevant disclosures and teachings of each of the cited and applied references are presented below.

Ochoa '353 teaches that both soluble and solid phase anti-CD3 antibodies are available for use, but only soluble phase antibodies are actually used in the embodiments.

Santamaria uses beads coated with anti-CD3 antibodies which are supposed to be solid phase. At page 6, first paragraph, Santamaria notes that "the interindividual differences in T cell expansion seem to be related to the sensitivity of the cells to the MAb rather than to the support used as MAb presenter (MNCs or beads)" and concludes that the range of T cells expansion depends on the cells.

Babbit does not teach whether the antibodies used are soluble or solid. Only anti-CD3 antibodies are used in the embodiments disclosed in Babbit. Furthermore, Babbit specifically teaches at column 12 under “Role of soluble OKT3” that "The OKT3 used in the process of the invention is preferably in solution rather than solid phase" by stating that one advantage (among what are assumed to be other advantages) of

using soluble OKT3 is that soluble OKT3 mediates a more physiological interaction between Fc-receptor-bearing accessory cells, e.g., monocytes, and T cells.

Ochoa '983 uses only soluble antibodies.

On the other hand, Wallace uses only IL-2 for activation of lymphocytes.

As the examiner continues to maintain, it can be understood in Ochoa '353 that both soluble and solid phase anti-CD3 antibodies are available for use. However, as discussed above, the use of soluble or solid phase antibodies are different in the six cited and applied references. On the contrary, within the range of the cited references, it can be said that the soluble phase is dominant. It is supposed that solid antibody is used in particular cases (the present invention examined this explicitly and set conditions). As described above, consideration of the purpose of use or cells of use, etc., is required to determine use of soluble or solid phase.

The examiner focuses only on a part of the description which shows merely one aspect and insists that one of ordinary skill in the art would use solid phase antibodies because a "suitable number of activated lymphocytes could be obtained at a faster rate". However, the common knowledge among those of skill in the art regarding this application shows variation. The

common knowledge maintained by the examiner is just one of the variations.

Attached hereto is a copy of Glickstein et al., *Journal of Immunology*, 156:2062-2067 (1996), which shows the state of the art at that time the present invention was made. In this attached reference, it is taught that cells become apoptotic and kill themselves as a result of using of solid phase anti-CD3 antibodies (see Fig. 1 which shows the response of hybridomas stimulated with soluble or plastic-bound anti-CD3 antibody.). This is a clear teaching away from using solid anti-CD3 antibodies that those of skill in the art would immediately recognize and understand.

In the Advisory Action, the examiner takes the position that "The key point is that the combination of solid phase anti-CD3 antibodies and IL-2 allow the activated T cells to maintain their activity without the presence of CMV antigen". In Santamaria, CMV seropositive PBMC are first stimulated for seven days by CMV to obtain CMV specific T cells. Thereafter, they are stimulated with anti-CD3 antibodies and IL-2 to make them available for long-term cultivation. In this regard, the present invention, which does not require specific antigen stimulation at any stage in cell preparation and which the examiner admits in the above quote, is distinctly different (a technique with a

different idea) from Santamaria. Therefore, the procedure in Santamaria, which stimulates PBMC with CMV is a strong disincentive towards the present invention for those skilled in the art from combination of Santamaria and Ochoa '353. Those of skill in the art who wish to stimulate and cultivate lymphocytes without specific antigen stimulation would not be motivated to use Santamaria whose basic idea is performed with a specific antigen.

In the Advisory Action, the examiner has also stated that "Wallace supports the assertion that activated T-cells from virally infected patients would be effective when reintroduced into said patient". Wallace however uses peripheral blood from an EBV seropositive healthy donor, not peripheral blood from an EBV patient. Antigen specific CTL obtained by stimulation with specific antigen is propagated with IL-2. The obtained cells (page 1013, 2.2) show *in vitro* killing effect against EBV transformed cells. In other words, Wallace shows an *in vitro* killing effect by antigen specific lymphocytes against cells which have same antigen.

As disclosed in the present specification at page 4, first paragraph, lines 8-12, HIV treatment performed by preparing HIV specific lymphocytes did not succeed. This means that the state of the art at the time the present invention was made

showed that antigen specific lymphocytes were not effective *in vivo*. Thus, the lymphocytes taught by Wallace, which present CTL activity *in vitro*, may not have any effectiveness *in vivo*. Therefore, considering the state of the art, because antigen specific lymphocytes do not show effectiveness in treatment against infectious diseases, those of skill in the art would not consider that "Wallace supports the assertion that activated T-cells from virally infected patients would be effective when reintroduced into said patient", as held by the examiner. Accordingly, as discussed above, the *in vivo* effectiveness of activated lymphocytes obtained from virally infected disease patients is still not clear.

Regarding the cited and applied Sekine reference, the examiner holds that "one of ordinary skill in the art is able to use elements in the prior art which are designed to solve different problems". Sekine refers to cancer treatment. However, the present specification, background and state of the art at page 2, second paragraph, lines 3-5 from the bottom and page 3, second paragraph, lines 1-5, clearly show that the etiology of cancer significantly differs from that of viral infection. Thus, those of skill in the art would not combine the other cited and applied references with Sekine.

Regarding Santamaria, the examiner states that "The preferred cultivation time does not exclude longer cultivating times and the ability to grow the T-cells long term does not preclude one from using the activated T-cells after a shorter period of time". Although Samatamaria's disclosure does not exclude a shorter cultivation time, those of skill in the art would reasonably expect success mainly with the preferable cultivation time.

The crux of the present invention is in using lymphocytes derived from virally infected patients for stimulation and proliferation. If lymphocytes from the blood of virally infected patients are cultivated, the risk of propagation of the virus itself is quite high. This would be recognized and understood by any one of ordinary skill in the art of immunology.

Wallace cultivates lymphocytes from the blood of a healthy man, whose serotype is EBV positive but in which EBV does not exist, and activates the lymphocytes by autologous EBV-transformed cells. Wallace discloses that activated lymphocytes could be administered to EBV infected patients. However, there is no presumption that lymphocytes should be cultivated from EBV infected patients themselves and then administered to them. Wallace may well recognize the risk involved.

Furthermore, Ochoa '983 cultivates lymphocytes from the blood of one twin who does not suffer from HIV and then administers the cultivated lymphocytes to another twin who suffers from HIV. Ochoa '983 does not presume, teach or suggest cultivating lymphocytes from the EBV or HIV infected patient himself and then administering the cultivated lymphocytes back either. Ochoa '983 may also well recognize the risk. Furthermore, although Santamaria cultivates lymphocytes from the blood of a CMV infected patient, Santamaria merely considers the possibility of cultivating specific CTLs *in vitro* long term but does not assume cultivation and administration of lymphocytes from virally infected patients. Santamaria may also recognize the risk of CMV contamination and so Santamaria uses cultivated lymphocytes from CMV-infected patient only for *in vitro* use and not *in vivo*.

Therefore, those of skill in the art would not be motivated at all to cultivate lymphocytes from EBV or CMV infected patients themselves for use in treatment and would instead believe that the technique may be lethal (by administration of the virus with the cultivated lymphocytes) rather than be effective in treatment. The present inventor went against the grain of what is commonly known and accepted in the art to arrive at the present invention.

Accordingly, the combination of the disclosures and teachings of the cited and applied references does not lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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